

**Claims:**

1. An isolated human epididymis-specific receptor protein-6 (HE6) polypeptide, comprising
  - i) the amino acid sequence encoded by SEQ ID NO: 1;
  - 5 ii) the amino acid sequence encoded by SEQ ID NO: 2;
  - iii) the amino acid sequence encoded by SEQ ID NO: 3;
  - iv) the amino acid sequence encoded by SEQ ID NO: 4;
  - v) the amino acid sequence encoded by SEQ ID NO: 5;
  - vi) the amino acid sequence encoded by SEQ ID NO: 6; or
  - 10 vii) the amino acid sequence encoded by SEQ ID NO: 7,  
or comprising a functional variant or functional fragment of an amino acid sequence of i) through vii).
2. An isolated polypeptide that comprises an amino acid sequence which has a  
15 sequence identity of at least 65%, 70-75%, 80-85%, 90-95% or 97-99% to one or more of the amino acid sequences i) through vii) of claim 1.
3. An isolated polypeptide of claim 1, which further comprises a heterologous sequence.  
20
4. An isolated polypeptide of claim 1, which comprises a polypeptide encoded by SEQ ID NO: 22 comprising the amino acid sequence as depicted in SEQ ID NO: 30.
- 25 5. An isolated polypeptide of claim 1, which comprises a polypeptide encoded by SEQ ID NO: 16-22, starting with AUG at nucleotide position 164-166 and terminating at stop codon at positions 3101-3103, 3143-3145, 3173-3175, 3167-3169, 3125-3127, or 3149-3151.
- 30 6. An isolated polypeptide encoded by SEQ ID NO: 16-22, starting at the codon at 2-4 and terminating at stop codon at positions 3101-3103, 3143-3145, 3173-3175, 3167-3169, 3125-3127, or 3149-3151.

-51-

7. An isolated polypeptide comprising, from N-terminus to C-terminus, the polypeptide sequence represented by amino acids 1 through 54 of SEQ ID NO: 22, covalently bound to the polypeptide X81892.
- 5    8. An isolated mouse epididymis-specific receptor protein-6 (ME6) polypeptide, comprising
  - i) the amino acid sequence encoded by SEQ ID NO: 9;
  - ii) the amino acid sequence encoded by SEQ ID NO: 10;
  - iii) the amino acid sequence encoded by SEQ ID NO: 11; or
  - iv) the amino acid sequence encoded by SEQ ID NO: 12;or comprising a functional variant or functional fragment of an amino acid sequence of i) through iv).
- 15    9. An isolated polypeptide that comprises an amino acid sequence which has a sequence identity of at least 65%, 70-75%, 80-85%, 90-95% or 97-99% to one or more of the amino acid sequences i) through iv) of claim 8.
- 10    10. An isolated polypeptide consisting essentially of amino acids 1 to 1009 of SEQ ID NO: 31.
- 20    11. An isolated polypeptide of claim 8 which comprises amino acid sequences encoded by SEQ ID NO: 9, 10, 11, 12 or 13, and further comprises a heterologous sequence.
- 25    12. An isolated polypeptide of claim 8, which comprises a polypeptide encoded by SEQ ID NO: 23, 24, 25, or 26, starting with AUG at nucleotide position 72-74 and terminating at stop codons 3099-3101, 3051-3053, 3090-3092, and 3018-3020.
- 30    13. An isolated polypeptide of claim 8, which comprises the sequence beginning with amino acid 1 of the sequence represented by SEQ ID NO: 31.

-52-

14. An isolated rat epididymis-specific receptor protein-6 (RE6) polypeptide, comprising

- i) the amino acid sequence encoded by SEQ ID NO: 13;
- ii) the amino acid sequence encoded by SEQ ID NO: 14; or
- 5 iii) the amino acid sequence encoded by SEQ ID NO: 15

or comprising a functional variant or functional fragment of an amino acid sequence of i) through iii).

15. An isolated polypeptide that comprises an amino acid sequence which has a

10 sequence identity of at least 65%, 70-75%, 80-85%, 90-95% or 97-99% to one or more of the amino acid sequences i) through iii) of claim 14.

16. An isolated polypeptide of claim 14 which comprises amino acid sequences encoded by SEQ ID NO: 13, 14, or 15, and further comprises a heterologous

15 sequence.

17. An isolated polypeptide of claim 14, which comprises a polypeptide encoded by SEQ ID NO: 27, 28, or 29, starting with AUG at nucleotide position 60-62 and terminating at stop codons 3099-3101, and 3015-3017.

20

18. An isolated polypeptide of claim 14, which comprises the sequence beginning with amino acid 1 of the sequence represented by SEQ ID NO: 32.

25 19. An isolated polynucleotide which encodes an HE6-polypeptide, or which encodes a functional variant or a functional fragment thereof, of claim 1.

20. An isolated polynucleotide which comprises the nucleotide sequence of

- i) SEQ ID NO: 1,
- ii) SEQ ID NO: 2,
- 30 iii) SEQ ID NO: 3,
- iv) SEQ ID NO: 4,
- v) SEQ ID NO: 5,
- vi) SEQ ID NO: 6, or

-53-

vii) SEQ ID NO: 7,

or a functional fragment or variant thereof, provided that said fragment comprises either SQ ID NO: 1, 2, 3, 4, 5, 6, or 7.

5 21. An isolated polynucleotide which comprises the nucleotide sequence of

i) SEQ ID NO: 9

ii) SEQ ID NO: 10,

iii) SEQ ID NO: 11, or

iv) SEQ ID NO: 12

10 or a functional fragment or variant thereof, provided that said fragment

comprises either SQ ID NO: 9, 10, 11, or 12.

22. An isolated polynucleotide which comprises the nucleotide sequence of

i) SEQ ID NO: 13,

15 ii) SEQ ID NO: 14, or

iii) SEQ ID NO: 15

or a functional fragment or variant thereof, provided that said fragment comprises either SQ ID NO: 13, 14, or 15.

20 23. Isolated polynucleotides of claim 20, 21, 22 which further comprise

heterologous sequences.

24. An isolated polynucleotide comprising from the 5' to the 3' terminus, an oligonucleotide consisting essentially of nucleotides 1-91 of SEQ ID NO: 16

25 covalently bound, in phase, to the polynucleotide X81892.

25. An isolated polynucleotide of claim 20, which comprises SEQ ID NOS:16, 17, 18, 19, 20, 21 or 22.

30 26. An isolated polynucleotide of claim 21, which comprises SEQ ID NOS: 23, 24, 25, or 26.

-54-

27. An isolated polynucleotide of claim 22, which comprises SEQ ID NOS:27, 28, or 29.

28. An isolated polynucleotide which comprises a nucleotide sequence that 5 codes without interruption for the polypeptide of SEQ ID NO: 30, or which comprises a nucleotide sequence that codes without interruption for a fragment or variant of the polypeptide of SEQ ID NO: 30, or a complement thereof.

29. Recombinant constructs comprising the polynucleotides of claim 20, 21, 22 10 operatively linked to a regulatory sequence.

30. A cell comprising a polynucleotide of claim 20 which expresses an HE-6 polypeptide.

15 31. A cell comprising a polynucleotide of claim 21 which expresses an ME-6 polypeptide.

32. A cell comprising a polynucleotide of claim 22 which expresses an RE-6 polypeptide.

20 33. A method of making epididymis-specific receptor-6 polypeptides, or functional fragments or variants thereof, comprising incubating a cell of claim 35-37 under conditions which allow expression of said polypeptides, fragments or variants, and recovering the polypeptides, fragments or variants.

25 34. An antibody or antigen-specific fragment specific for a polypeptide comprising amino acid sequences of claims 1, 8, and 14.

30 35. An antibody according to claim 34, wherein said antibody is a monoclonal antibody.

36. A pharmaceutical composition comprising an antagonist or inhibitor of a polypeptide comprising amino acid sequences encoded by SEQ ID NO: 1, 2, 3,

-55-

4, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, or 22 and a pharmaceutically acceptable carrier.

37. A pharmaceutical composition comprising an antisense nucleotide which  
5 can bind with any of the nucleotide sequences shown in SEQ ID NO: 1, 2, 3, 4,  
5, 6, 7, 8, 16, 17, 18, 19, 20, 21, or 22 and a pharmaceutically acceptable carrier.

38. A pharmaceutical composition comprising an antibody of claim 34 and 35  
10 and a pharmaceutically acceptable carrier.

39. A pharmaceutical composition for treating a male reproductive disorder comprising administering an effective amount of a polypeptide comprising amino acid sequences encoded by SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 16, 17, 18, 19, 20,  
15 21, or 22.

40. A pharmaceutical composition for diagnosing a male reproductive disorder comprising administering an effective amount of a polypeptide comprising amino acid sequences encoded by SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 12, 13, 14, 15, 27,  
20 28, or 29.

41. A method of isolating an agent which modulates expression activity of an epididymis-specific receptor of claim 1, 8, or 14, or of a polynucleotide which encodes it, comprising incubating said epididymis-specific receptor or  
25 polynucleotide with a putative agent, and measuring the amount of activity of said receptor or polynucleotide.

42. The method of claim 41 wherein said agent is an antisense oligonucleotide according to claim 37.

30 43. The method of claim 41 wherein said agent is a ligand of said receptor.

-56-

44. A method for isolating a ligand specific for an epididymis-specific receptor of claim 1, 9, or 14, comprising contacting the epididymis-specific receptor with a substance suspected to be a ligand of said receptor and detecting binding of said receptor to said ligand.

5

45. The method of claim 41-44, wherein the said agent or ligand is an agonist of the epididymis-specific receptor.

10 46. The method of claim 41-44, wherein the said agent or ligand is an antagonist of the epididymis-specific receptor.

47. The method of claim 41-44, wherein the said agent or ligand is an antibody or polypeptide.

15 48. The method of claim 41-44, wherein the said agent or ligand is a small molecule which binds to the epididymis-specific receptor.

20 49. A method for diagnosing infertility in a male mammal, which is associated with under-expression or over-expression of a polynucleotide comprising a sequence of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, or 22, comprising contacting a tissue, cell, or polynucleotide from said male with a probe that is specific for said SEQ ID and determining the amount of nucleic acid that hybridizes to the probe wherein said cell or tissue is from a biopsy sample or thin section from the epididymis of said male mammal.

25

50. A method for diagnosing infertility in a male mammal comprising measuring antibodies from said male specific for a polypeptide comprising a sequence of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21 or 22.

30 51. A method for treating infertility in a male mammal comprising administering to said mammal an agonist or antagonist of an epididymis-specific receptor comprising administering an effective amount of a polypeptide comprising amino

-57-

acid sequence encoded by SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 16, 17, 18, 19, 20,  
21 or 22.

52. A method for contraception in a male mammal comprising administering to  
said mammal an antagonist of an epididymis-specific receptor comprising a  
polypeptide encoded by SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21  
or 22.

10 53. A recombinant construct comprising the polynucleotide of SEQ ID NO:33  
operatively linked to a regulatory sequence.

54. An antibody or an antigen-specific fragment specific for human HE6  
polypeptide comprising amino acid sequences encoded by SEQ ID NO:33.

15 55. A pharmaceutical composition comprising an antagonist or inhibitor of a  
polypeptide comprising amino acid sequences encoded by SEQ ID NOS: 34 or  
35.

20 56. A pharmaceutical composition for treating a male reproductive disorder  
comprising administering an effective amount of a polypeptide comprising an  
amino acid sequence encoded by SEQ ID NO:33.

25 57. A composition for diagnosing a male reproductive disorder comprising  
administering an effective amount of a polypeptide comprising amino acid  
sequences encoded by SEQ ID NO:33.

58. Isolated proteins encoded by DNA of any of the claims 25, 26, 27,  
comprising the amino acid sequences of SEQ ID NO 36-60.